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Variation of Serum PSA Levels in COVID-19 Infected Male Patients with Benign Prostatic Hyperplasia (BPH): A Prospective Cohort Study

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OBJECTIVE	To investigate the effect of SARS CoV-2 on serum total PSA levels in men with BPH diagnosed with COVID-19.
METHODS	The PSA (Kit: Immunoassay Program- Cycle 18, Siemens Atellica IM Analyzer) levels in patients who had had a PSA check at least 3 months, but no more than 6 months, prior to diagnosis of acute COVID-19 infection, were examined retrospectively. PSA levels were measured and recorded from these patients on the first day of diagnosis of COVID-19. These patients were called back for urology outpatient follow-up at the third month after the end of the COVID-19 treatment. PSA levels measured in the pre-COVID-19 period, during the period of active infection with COVID-19, and in the post-COVID-19 period were compared.
RESULTS	In total, 91 patients had a serum PSA level of 1.58 ± 1.09 ng/mL in the pre-COVID-19 period, a serum PSA level of 4.34 ± 3.78 ng/mL measured in the COVID-19 period and 2.09 ± 2.70 ng/mL in the post-COVID-19 period. It was determined that the serum PSA level measured during active COVID-19 infection was statistically significantly higher than the PSA levels measured according to the pre-COVID-19 period and the post-COVID-19 period ($P < .001$, $P < .001$; respectively).
CONCLUSION	SARS-CoV-2 infection in men diagnosed with BPH causes significant increases in PSA levels during the active period of the disease. Measurement of PSA values used in the diagnosis, differential diagnosis, and follow-up of prostate diseases in the acute period of infection and in the early period after infection treatment may cause false evaluations that may affect the diagnosis and treatment steps of prostate diseases in these patients. UROLOGY 159: 16–21, 2022. © 2021 Elsevier Inc.

Cases of pneumonia caused by a newly identified virus began to be reported on 31.12.2019 in Wuhan, China.¹ The disease was defined as Corona Virus Disease 2019 (COVID-19) on 20.02.2020 by the World Health Organization (WHO). According to the data from Johns Hopkins Coronavirus Resource Center, as of June 13, 2021, severe acute respiratory syndrome

coronavirus-2 (SARS-CoV-2) has caused more than 175 million cases of COVID-19, and more than 3.5 million deaths.²

Although SARS-CoV-2 was thought to be a virus targeting only the lung in the early stages of the pandemic, over time, it has been concluded that all tissues expressing the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2), which allows SARS-CoV-2 to dock with the host cell, may be possible targets of the virus.³ In a recent study, it has been shown that in addition to the ACE2 protein, SARS-CoV-2 uses the transmembrane protease serine 2 (TMPRSS2) to enter into the host cell, and spread.⁴ It has been shown that these proteins are expressed in many different tissues such as the lung, colon, liver, kidney, as well as in the prostate.⁵ Although only a few data have been reported on prostate involvement among male patients with COVID-19, the prostate appears to be a putative target of SARS-CoV-2.

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Prostate-specific antigen (PSA) is a single-chain, glycoprotein molecule with serine protease activity.⁶ Immunohistochemical studies have shown that PSA is mainly found in the cytoplasm of prostatic acinar cells and the ductal epithelium.⁷ As PSA is synthesized in malignant cells, it can also be synthesized in benign conditions such as aging, benign prostatic hyperplasia (BPH), prostatitis and prostate infarction, where the structure of the prostate tissue is disrupted. For this reason, an increase in serum PSA levels can be observed not only in malignant conditions, but also in benign conditions. PSA is accepted to be not a cancer-specific protein, but an organ specific protein, that is, prostate tissue.⁸ Currently, the serum PSA level measured in clinical practice is still the most frequently used by clinicians among urological tests in pathologies where the prostate tissue is affected.⁹ For this reason, PSA is considered a prostate tissue-specific protein, not cancer-specific. However, in clinical practice, serum PSA levels are frequently used by clinicians in prostate diseases. We hypothesize that PSA may be elevated (due to ACE2) in COVID-19-infected patients with BPH, and therefore the acute COVID-19 pandemic period may be an unreliable time frame to use PSA as a tumor marker. In our study, we aimed to investigate the effect of COVID-19 on serum total PSA levels in men diagnosed with COVID-19.

MATERIALS AND METHODS

Local ethics committee approval was obtained for this study with the decision number 37732058-514.10 dated December 7, 2020. Patients who had been diagnosed with COVID-19 and followed-up and treated in the Health Sciences University Erzurum Regional Training and Research Hospital between January 2021 and June 2021 were included in the study.

Patients who were over 40 years of age, those treated on an outpatient - or inpatient - basis due to active COVID-19 infection, those previously examined in the urology outpatient clinic

for lower urinary system symptoms and diagnosed as benign prostatic hyperplasia (BPH), those that were uncomplicated cases, those with no indication for surgical treatment for whom conservative follow-up was planned, those treated with medical or medical treatment options, those whose serum total PSA levels were recorded in the patient files in the last 3-6 months, and those who were in the routine outpatient follow-up program were included in the study.

The diagnosis of BPH is made as follows in our institution: After a detailed medical history is taken from patients over the age of 40 who present to the urology outpatient clinic due to lower urinary tract symptoms, a Turkish-validated symptom score scale (IPSS) is filled in, uroflowmetry is performed, and the serum PSA values of the patients are measured (PSA <4 ng/mL). All these parameters are evaluated and based on the diagnosis and code list of the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) published by the Ministry of Health of the Republic of Turkey; the diagnosis code N40.0 (BPH) is entered into the system for these patients. We included patients who were examined for lower urinary tract symptoms and diagnosed with BPH and had a diagnosis code of N40.0 in the system.

The PSA (Kit: Immunoassay Program- Cycle 18, Siemens Atellica IM Analyzer) levels in patients who had had a PSA check at least 3 months, but no more than 6 months, prior to diagnosis of acute COVID-19 infection, were examined retrospectively. Serum PSA levels were measured and recorded from these patients on the first day of diagnosis of COVID-19. These patients were called back for urology outpatient follow-up at the third month after the end of the COVID-19 treatment with reference to studies showing that the transient PSA elevation in benign diseases of the prostate regressed to the normal level at the third month, and their PSA levels were measured and recorded.¹⁰⁻¹² Serum PSA levels measured in the pre-COVID-19 period, during the period of active infection with COVID-19, and in the post-COVID-19 period were statistically compared.

SARS-CoV-2 infection was determined by pharyngeal and/or nasal swab positivity using real-time-polymerase chain reaction (RT-PCR). Patients with 2 consecutive positive PCR tests were considered positive for COVID-19.

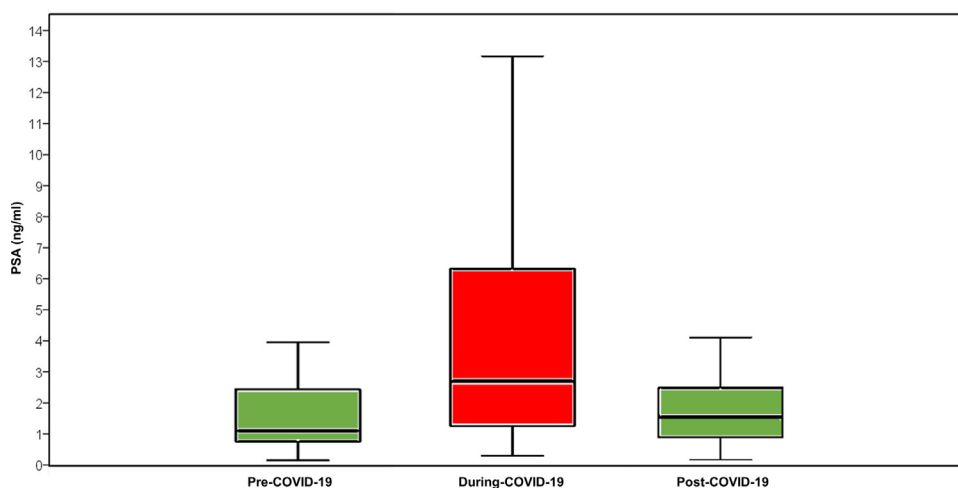


Figure 1. Presentation of PSA values with box-plots in the pre-COVID-19, active infection and post-COVID-19 periods, respectively. (Color version available online.)

The patients included in the study were divided into 3 groups: Group 1: Patients who had positive PCR results for COVID-19 and completed their treatment in isolation at home; Group 2: Patients who had moderate illness with clinical signs of pneumonia, but with no signs of severe pneumonia (Severe pneumonia: Pneumonia fitting any one of the following conditions: respiratory rate ≥ 30 breaths/min; SpO₂ $\leq 92\%$; lung infiltration rate of $>50\%$ and patients treated at the hospital); Group 3: Patients with severe illness hospitalized with severe pneumonia and who developed macrophage activation syndrome in their follow-up. The serum PSA levels were measured before COVID-19 infection, during active infection, and at the third month after the treatment of COVID-19 infection in the patients in these groups, and they were compared. As a result of the chest computed tomography (Brand: Toshiba Aquilion 64) performed on the patients, positive radiological findings (unilateral or bilateral ground glass images, parenchymal consolidation) related to SARS-CoV-2 infection were examined, and reported by the same radiologist. Informed consent was obtained from all patients included in the study.

Patients under the age of 40, patients whose serum PSA level measured in the last 6 months was unknown, patients with suspected malignancy on the physical examination, and radiological imaging, patients who were scheduled for further examination because the serum PSA level measured in the last 6 months was above 4 ng/mL, hospitalized patients with transurethral catheter for urological or non-urological reasons such as urinary retention before PSA measurement, patients with a history of prostate cancer, those with a history of drug use that may affect the PSA level (LHRH agonist, 5-alpha reductase inhibitor, etc), patients with a history of invasive interventional procedure to the prostate after PSA measurement 3-6 months before the active infection and before the PSA measurement at the third month after the end of the infection treatment, patients who did not present to the outpatient clinic control at the third month after the end of the treatment, active infection in the third month after the end of the treatment, and patients who died during the study were excluded from the study. The flow chart of the patients included and excluded from the study has been displayed in Figure supp.

STATISTICAL ANALYSIS

Categorical data were presented as numbers and percentages. Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum). Mean differences between more than 2 independent groups of normally distributed data were compared with one-way ANOVA. Mean differences between more than 2 dependent groups of were compared with repeated measures ANOVA. Bonferroni correction was used in pairwise comparison of more than 2 groups with statistically significant differences.

Statistical significance was considered when *P* value was considered when *P* value was $<.05$.

RESULTS

The study included 91 patients who fulfilled the study criteria. The mean age of the 91 patients included in the study was 68.1 ± 9.08 years and the mean BMI was 23.6 ± 1.94 kg/m². The

mean hospital stay of the patients was 7.92 ± 6.97 days. The most frequently observed symptoms in the patients were fever (59.2%), cough (55.1%), dyspnea (45.6%), tachypnea (48.3%), weakness-fatigue (47.2%), myalgia (43%), headache (39.1%), sore throat (36.9%), gastrointestinal symptoms (31%), and loss of smell (21%), respectively.

The demographic and clinical characteristics of the patients and the serum PSA levels measured before, during, and after COVID-19 have been demonstrated in Table 1.

It was determined that patients with recorded serum PSA levels in the pre-COVID-19 period initially presented to the urology outpatient clinic for lower urinary tract symptoms for 124.2 ± 32.3 days on average before the treatment, and in the post-COVID-19 period, patients were detected to present to the urology outpatient clinic for control PSA measurement 86.2 ± 7.3 days after the end of their treatment.

In total, 91 patients had a serum PSA level of 1.58 ± 1.09 ng/mL in the pre-COVID-19 period, a serum PSA level of 4.34 ± 3.78 ng/mL measured in the COVID-19 period and 2.09 ± 2.70 ng/mL in the post-COVID-19 period. It was determined that the serum PSA level measured during active COVID-19

Table 1. Demographic and clinical characteristics of the patients and serum total PSA levels

Characteristic	
COVID-19 patients, n (%)	91 (100)
Age, (years)	
Mean \pm SD	68.1 ± 9.08
Median (range)	69 (43-86)
BMI, kg/m ²	
Mean \pm SD	23.6 ± 1.94
Median (range)	24 (20-30)
Pre-COVID-19 period PSA, ng/mL	
Mean \pm SD	1.58 ± 1.09
Median (range)	1.12 (0.18-3.95)
During COVID-19 period PSA, ng/mL	
Mean \pm SD	4.34 ± 3.78
Median (range)	2.80 (0.32-18.1)
Post-COVID-19 period PSA, ng/mL	
Mean \pm SD	2.09 ± 2.70
Median (range)	1.80 (0.19-24.0)
Length of stay in hospital (days)	
Mean \pm SD	7.92 ± 6.97
Median (range)	9 (0-25)
No chest CT, n (%)	24 (26.4)
Chest CT involvement, n (%)	
No involvement	15 (16.5)
50% less involvement	19 (20.9)
50% > more involvement	33 (36.3)
COVID-19 severity, n (%)	
Group 1 (Mild severe)	30 (33.0)
Group 2 (Moderate)	26 (28.6)
Group 3 (Severe)	35 (38.5)
Medical treatment options for BPH n (%)	
Alpha blocker,	71 (78.0)
Alpha blocker + AA	15 (16.5)
PDE5I	5 (5.5)
Management of COVID-19 patients, n (%)	
Inpatients	59 (64.8)
Outpatients	32 (35.2)

COVID-19, Coronavirus disease-19; SD, standard deviation; BMI, body mass index; PSA, prostate specific antigen; BPH, benign prostatic hyperplasia; PDE5I, phosphodiesterase 5 inhibitors; AA, antimuscarinic agents; CT, computer tomography.

Table 2. Comparative results of serum PSA values of patients pre-COVID-19 period, during the period of active infection with COVID-19, and post-COVID-19 period

Variables	Pre-COVID-19 period (1) (Mean \pm SD)	During COVID-19 period (2) (Mean \pm SD)	Post-COVID-19 period (3) (Mean \pm SD)	P-value
PSA (ng/mL)	1.58 \pm 1.09	4.34 \pm 3.78	2.09 \pm 2.70	<0.001* 1 vs 2 <0.001 1 vs 3 0.165 2 vs 3 <0.001

* Repeated measures ANOVA.

COVID-19, Coronavirus disease-19; SD, standard deviation; PSA, prostate specific antigen.

Table 3. Comparative results of serum PSA levels in mild, moderate and severe patient groups in the pre-COVID-19 infection period, COVID-19 active infection period, and post-COVID-19 treatment period

COVID-19 Severity				
Variables	Group 1 (Mild) (Mean \pm SD)n = 30	Group 2 (Moderate) (Mean \pm SD)n = 35	Group 3 (Severe) (Mean \pm SD)n = 35	P-value
Pre-COVID-19 period PSA (ng/mL) (1)	1.39 \pm 1.08	1.79 \pm 1.15	1.53 \pm 1.01	.336*
During COVID-19 period PSA (ng/mL) (2)	3.88 \pm 3.92	4.35 \pm 3.71	4.88 \pm 3.79	.621*
Post-COVID-19 period PSA (ng/mL) (3)	1.85 \pm 1.74	2.55 \pm 3.92	1.75 \pm 1.21	.446*
P-value	<0.001† 1 vs 2 0.003 1 vs 3 0.384 2 vs 3 0.006	<0.001† 1 vs 2 <0.001 1 vs 3 0.684 2 vs 3 0.025	<0.001† 1 vs 2 <0.001 1 vs 3 0.731 2 vs 3 <0.001	

COVID-19, Coronavirus disease-19; SD, standard deviation; PSA, prostate specific antigen.

* One way ANOVA.

† Repeated measures ANOVA.

infection was statistically significantly higher than the PSA levels measured according to the pre-COVID-19 period and the post-COVID-19 period ($P < .001$, $P < .001$; respectively). It was observed that there was no significant difference between the serum PSA level measured before COVID-19 and the serum PSA level measured after COVID-19 ($P = .102$) (Table 2) Fig. 1(Supplementary Figure 1).

Of the 91 patients with a diagnosis of COVID-19 included in the study, 30 (33%) were in the mild, 35 (38.5%) moderate, and 26 (28.6%) severe patient group.

The serum PSA levels measured in the pre-COVID-19 period were as follows: 1.39 \pm 1.08 ng/mL in mild severity patients, 1.79 \pm 1.15 ng/mL in moderate severity patients and 1.53 \pm 1.01 ng/mL in severe patients. No significant difference was observed between the serum PSA levels measured between the groups in the pre-COVID-19 period ($P = .336$).

The serum PSA levels measured during the COVID-19 period were as follows: 3.88 \pm 3.92 ng/mL in mild severity patients, 4.35 \pm 3.71 ng/mL in moderate severity patients, and 4.88 \pm 3.79 ng/mL in severe patients. No significant difference was observed between the serum PSA levels measured between the groups during the COVID-19 period ($P = .621$).

The serum PSA levels measured in the post-COVID-19 period were as follows: 1.85 \pm 1.74 ng/mL in mild severity patients, 2.55 \pm 3.92 ng/mL in moderate severity patients, and 1.75 \pm 1.21 ng/mL in severe patients. No significant difference was observed between the serum PSA levels measured between the groups in the post-COVID-19 period ($P = .446$) (Table 3).

DISCUSSION

Although COVID-19 was considered to be a disease involving the respiratory system in the early stages of the epidemic, it was accepted as a multi-systemic disease in later studies.¹³ Over time, organs other than the lung have also been identified as targets of SARS-CoV-2.⁴ After SARS-CoV-2 binds to the ACE2 receptor, an enzyme called TMPRSS2 separates the spike protein from the virus, allowing the virus to fuse with the cell membrane and thus the virus to enter the cell.¹⁴ The high level of expression of ACE2 receptors in organs such as lungs, heart, kidneys and the liver, and the similar high expression in the prostate makes the prostate one of the reservoir organs of the virus.¹⁵ In addition, studies have shown that the TMPRSS2 gene is highly expressed in human prostate epithelial cells.¹⁶ The presence of the ACE2 receptor and TMPRSS2 in the human prostate, as well as the regulation of TMPRSS2 by androgens, make the prostate a potential target organ in SARS-CoV-2 infection.^{5,14,17}

PSA is a single-chain, glycoprotein molecule. PSA (also known as hK3), a member of the tissue kallikrein family, has serine protease activity. PSA is synthesized by prostate epithelial cells as a prepro-protein consisting of 261 amino acids.⁶ PSA is the most reliable biochemical marker used in the diagnosis and follow-up of prostate diseases in clinical applications.⁸ Although PSA is prostate specific, it is not considered cancer specific. Pathologies

that cause deterioration in the prostate structure such as physiological conditions, urological interventions, and infection can also cause changes in the serum PSA level.¹⁸ It is known that serum PSA levels increase in cases where basal cells are lost in the prostate tissue, the integrity of the basement membrane is impaired, and the normal luminal structure is damaged.⁹

We conducted this prospective cohort study on 91 COVID-19-infected male patients with known serum PSA levels, followed up with a diagnosis of BPH. In this study, we aimed to investigate the effects of SARS-CoV-2 on the prostate, a potential target organ, by focusing on the changes in serum PSA levels in the pre-COVID-19 period, the period with active COVID-19 infection, and the period after the treatment of COVID-19 infection. We found that the serum PSA levels measured in the active period of the disease were statistically significantly higher than the serum PSA levels measured before and after the disease ($P < .001$, $P < .001$; respectively). We determined that there was no statistically significant difference between the mean PSA levels before and after treatment ($P = .165$). The results of this study, which is the first study in the literature to compare the serum PSA levels of male patients with a diagnosis of COVID-19 (measured in the pre-COVID-19, active infection period and the post-COVID-19 infection period), supports the hypotheses in the other studies in the literature that the prostate is a potential target organ of SARS-CoV-2 and that the infection can cause damage to the prostate tissue by various mechanisms. Although ACE2 and TMPRSS2 are highly expressed in prostate tissue, the prostate is one of the potential target organs in SARS-CoV-2 infection, and COVID-19 infection is thought to affect prostate tissue through various mechanisms, to our knowledge, there is no study in which changes in serum PSA levels have been measured during COVID-19 infection, and PSA has been monitored at various stages of the disease.

It has been shown that SARS-CoV-2 can cause tissue damage in the prostate by many possible mechanisms.¹³ ACE-2 is an enzyme that has anti-inflammatory, anti-fibrotic and vasodilator effects by modulating the effects of angiotensin II (Ang-II), which has proliferative and inflammatory properties. Ang-II is found in the epithelial basal layer of the prostate and its expression is significantly increased in BPH.^{19,20} SARS-CoV-2 is known to cause down-regulation of ACE2.²¹ Thus, suppression of ACE2 in SARS-CoV-2 infection provides evidence that it can activate pro-inflammatory pathways, increase cytokine release, and ultimately cause inflammatory responses in sensitive organs such as the prostate.¹³ We think that the increased expression of Ang-II in the prostate in BPH patients may increase the effects of SARS-CoV-2 on the prostate, especially in these patients. These mechanisms may explain the elevation in serum PSA levels during the active phase of COVID-19 disease in male patients with BPH.

It is known that SARS-CoV-2 infection can cause micro- and macro-vascular complications in many

organs.²² Studies examining the effects of SARS-CoV-2 infection on the prostate are very limited in the literature and generally consist of case reports. Duarte et al. reported in their case report that they detected thrombus in small vessels and diffuse ischemic infarction in the radiological imaging and then in the histologic examination of the postoperative prostate material of a 71-year-old patient with BPH, who was infected with SARS-CoV-2.²³ In this case report, the authors reported that SARS-CoV-2 infection increased the thrombogenic status in the prostate and the development of ischemic infarction, with reference to studies that showed that SARS-CoV-2 is a systemic procoagulant, and has a tendency to increase the disseminated intravascular coagulation (DIC) status.²³ We believe that micro- or macro-vascular complications that may cause ischemic infarction in the prostate in SARS-CoV-2 infection should be evaluated to have been caused by a different mechanism that can explain the increase in serum PSA levels observed in the active period of COVID-19 disease in male patients with BPH by contributing to the deterioration of tissue nutrition in the prostate.

Although there is no study in the literature examining the change in serum PSA level by COVID-19, Vincenzo et al. evaluated serum PSA levels in patients with COVID-19 in a clinical observation.²⁴ In this study, the serum PSA levels of 23 consecutive patients diagnosed with COVID-19 with a mean age of 57.1 years were measured once from each patient, and the mean serum PSA levels of the patients were found to be 1.13 ng/mL. In the results of the study, the authors were content in reporting that serum PSA levels in patients with COVID-19 were within the normal range.²⁴ It is important that the study focused on serum PSA levels in COVID-19 patients and contributed to the literature in this sense. However, the results of this study do not provide information about the change in serum PSA levels in COVID-19 patients. In addition, the study has limitations such as the fact that the serum PSA value was measured only once from each patient, the serum PSA levels were not known before and after the COVID-19 infection, the previous urological histories of the patients were unknown, and that the study included a small group of patients. These limitations do not make it possible to evaluate the change in serum PSA levels in patients with COVID-19. In our study, the comparison of serum PSA levels of the same patient in the pre-COVID-19, COVID-19 period and post-COVID-19 periods, the high number of our cases and the knowledge of the urological histories of the patients were important in evaluating the results of our study and the PSA change in male patients infected with COVID-19.

The limitations of our study can be listed as includes only patients with a diagnosis of BPH, the absence of a control group, absence of patients prostatitis symptoms and urine culture results, the absence of histopathological results of the prostate, not evaluating PSA isoforms. Despite these limitations, our study will take its place as the first study in the literature showing that serum PSA

levels may increase in patients with BPH in the acute phase of the disease during such a pandemic period and warn clinicians to be more careful in PSA interpretations during this acute infection period. Acute COVID-19 infection appears to be associated with small/moderate elevations in serum PSA in patients with known BPH. Therefore, PSA readings made during the acute infection period should be interpreted with caution.

CONCLUSION

COVID-19 infection causes elevations in serum PSA levels in men with BPH. Measurement of PSA values used in the diagnosis, differential diagnosis, and follow-up of prostate diseases in the acute period of infection and in the early period after infection treatment may cause false evaluations that may affect the diagnosis and treatment steps of prostate diseases in these patients. We believe that the results of our study will guide clinicians using PSA in the evaluation of prostate diseases, in their patients infected with COVID-19, or in the early stages of the treatment of COVID-19 infection. Further prospective, randomized studies with large series including histopathological changes targeting the understanding of the physiopathology will contribute to the literature.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2021.09.016>.

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